Obscure Gastrointestinal Bleeding

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Introduction

In last decade, the availability of advanced diagnostic innovations like capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE) have led to reclassification of gastrointestinal (GI) bleeding into three categories: upper, mid- and lower GI bleeding. If the source of GI bleeding is between the ampulla of Vater and the terminal ileum, it is designated as mid-GI bleeding.

Of total GI bleeding, it is estimated that upper GI bleeding (from the esophagus to duodenum 2nd portion), lower GI bleeding (from the colon and anorectum) and mid GI bleeding account, respectively, for 50%, 40% and 10%. Obscure gastrointestinal bleeding (OGIB) is defined as occult or overt bleeding of unknown origin that persists or recurs after an initial negative endoscopic evaluation including colonoscopy and EGD. Overt OGIB is defined as visible GI bleeding (e.g., melena or hematochezia) and can be categorized further as active (i.e., evidence of ongoing bleeding) versus inactive bleeding. In this review, we will discuss the etiology and current diagnostic approach focused on the CE and BAE in patients with OGIB.

Etiology of OGIB

Recent advance of CE and BAE have led to better understanding of the etiological profile of small bowel bleeding and there is a paradigm shift in the management of small bowel bleeding, with the majority of cases now being treated nonsurgically.

A variety of lesions may result in small bowel bleeding, with the etiology of bleeding being different in various age groups (Table 1). Zhang et al. studied 385 OGIB patients and found that, in elderly patients (>65 years), vascular anomalies (54.35%), small intestinal ulcer (13.04%), small intestinal tumors (11.96%) were the common cause of small intestinal bleeding; in middle age (41-64 years) vascular anomalies (34.82%), small intestinal tumors (31.25%), nonspecific enteritis (9.82%) were the major causes and in young adults (<40 years), the leading causes were Crohn’s disease (34.55%), small intestinal tumors (23.64%) and nonspecific enteritis (10.91%). SB lesions account for the majority of the etiologies of OGIB (∼75%) and predominantly include vascular lesions (∼70%) in the Western pop-

| Table 1. Etiology of Obscure Gastrointestinal Bleeding According to Age |
|-----------------------------|-----------------------------|-----------------------------|
| Elderly (>65 years)         | Middle-Aged (41-65 years)   | Young Adult (17-40 years)   |
| Vascular anomalies          | Vascular anomalies          | Crohn’s disease             |
| Small intestinal ulcer      | Small intestinal tumours    | Small intestinal tumours    |
| NSAID enteropathy           | Non-specific enteritis      | Meckel’s diverticulum       |
| Small intestinal tumours    | Small intestinal ulcer      | Non-specific enteritis      |
| Non-specific enteritis      |                            | Dieulafoy’s lesion          |
|                            |                            | Vascular anomalies          |
ulation and ulcerations (~45%) in the Asian population. Because there has been reported discrepancy of etiology between the race and ethnicity, it is necessary to identify the etiology of OGIB in Korean.

**Evaluation of Obscure Gastrointestinal Bleeding**

A detailed history and physical examination can provide important clues to the underlying etiology, but endoscopic evaluation remains the cornerstone of the diagnosis and management of OGIB. In patients with occult OGIB, it is important to exclude malabsorption and hematologic causes of anemia, and document objective evidence of GI bleeding. A thorough small bowel examination is important, as 2-10% of these patients have been reported to have underlying tumors, of which the majority appear to be malignant. The main limitations of SB evaluation in the past were related to its length (>6 m) and the limited intubation depth with conventional endoscopy, as well as the low sensitivity of traditional radiologic tests for detection of flat mucosal lesions such as angioectasias.

These shortcomings have been overcome by recent developments in both endoscopic techniques, such as CE and BAE, and radiologic techniques, such as CT/MR enterography or enteroclysis. These advances in small bowel diagnostics, as well as the capacity to successfully perform endoscopic therapeutic interventions using BAE, have largely replaced surgical procedures (intraoperative enteroscopy, laparoscopy, and exploratory laparotomy), resulting in a trend toward noninvasive evaluation and management of OGIB.

Details pertaining to clinical presentation (eg, presence or absence of overt bleeding), nature of bleeding (eg, hematemesis, hematochezia, or melena), bleeding diathesis (eg, von Willebrand disease), medication use (eg, aspirin or nonsteroidal anti-inflammatory drugs), comorbidities (eg, valvular heart disease, vasculitis, or amyloidosis), prior procedures/surgeries (eg, liver biopsy, liver transplantation, abdominal aortic aneurysm repair, or bowel resection), prior radiation therapy, and family history (eg, inflammatory bowel disease or polyposis syndromes) may provide important clues to the underlying etiology of OGIB. Physical examination, including a detailed dermatologic evaluation, may also be useful in the diagnosis of systemic syndromes (eg, hereditary hemorrhagic telangiectasias, amyloidosis, and blue-rubber bleb nevus syndrome).

**Capsule endoscopy (CE)**

CE enables visualization of the entire small intestine but lacks the potential for therapeutic intervention. Recent meta-analysis showed that the pooled diagnostic yield for CE was 62% (95% confidence interval [CI], 47.3-76.1) and compared with the criterion standard of intraoperative enteroscopy for detecting a bleeding source, CE had a sensitivity of 95% and specificity of 75% in a prospective, two-center study of 47 patients. High diagnostic yields (91.9%) for urgently performed CE (ie, within 48 hours after admission) in patients with mild to moderate acute overt OGIB suggest that early intervention with CE may enhance diagnostic effectiveness. If the CE study fails to identify the cause of OGIB, a second CE study may be considered. In a prospective study of 76 patients with persistent OGIB and a nondiagnostic CE, a “second look” CE was positive in 49% of patients. The second CE was more likely to be diagnostic when a patient’s clinical course changed from occult to overt bleeding or if the hemoglobin level dropped >4 g/dL. Benefits of CE include the noninvasive nature of the test, patient acceptance, safety, and diagnostic yield. Limitations of CE include inability to provide therapy or precisely locate a lesion, false-positive results, the potential for erratic passage resulting in missed lesions, and limited battery life of the equipment causing incomplete studies. The primary risk of CE is retention, occurring in 1.4% of CE examinations in one large study. If significant lesions are detected on CE, the patient should be referred for specific management of these findings.
Rebleeding rates after a negative CE study are generally low (6%-11%). However, recent study using Korean capsule registry database reported that overall rebleeding rate was 19.0% during a mean follow-up of 38.7 months and rebleeding rate did not differ by positive CE results or application of interventional treatment. CE did not have a significant impact on the long-term outcome of patients with OGIB. Patients with angiodysplasia on CE or OGIB>3 months need to be closely followed even after interventional treatment. In patients who are taking anticoagulants, discontinuation of drugs is necessary in order to lower the risk of rebleeding.

Balloon-Assisted Enteroscopy (BAE)

BAE utilizes the principle of push-and-pull enteroscopy and is comprised of double-balloon enteroscopy (DBE) and single-balloon enteroscopy (SBE). DBE consists of an enteroscope and an overtube, both of which have balloons at their distal ends, as its name suggests. In comparison, SBE consists of an enteroscope and an overtube, with a balloon on only the overtube. The balloons on the double-balloon enteroscope and overtube are composed of latex, whereas the balloon on the single-balloon overtube is made of silicon. The enteroscope in both systems has a working length of 200 cm, and the overtube is 140 cm in length. The outer diameter is 9.4 mm on the double-balloon enteroscope and 9.2 mm on the single-balloon enteroscope.

In multiple large studies of patients with OGIB who underwent BAE, the diagnostic yield ranged from 43% to 81%. Recent meta-analysis demonstrated the yield for DBE performed after a previously positive CE was 75.0% (95% CI 60.1-90.0), with the odds ratio for successful diagnosis with DBE after a positive CE compared with DBE in all patients of 1.79 (95% CI 1.09-2.96; P = 0.02). In contrast, the yield for DBE after a previously negative CE was only 27.5% (95% CI, 16.7-37.8). Treatment success rates of between 43% and 84% have been reported.

A modeled cost-minimization analysis of the management of occult OGIB proposed BAE as the most cost effective initial test after standard endoscopy if the goal is treatment or definitive diagnosis. Another model suggested that initial BAE was a cost-effective approach for patients with OGIB who likely have angiectasias in the small bowel accessible with a single antegrade approach.

Management of OGIB

The management of patients with OGIB should be individualized based upon several important factors, including clinical presentation (obscure versus occult OGIB), type of bleeding (melena or hematochezia), duration and frequency of bleeding, severity and acuity of bleeding, need for packed red blood cell (pRBC) transfusions, presence or absence of iron-deficiency anemia, and associated clinical symptoms (abdominal pain and/or weight loss). As medical management has not been shown to be effective in the long-term management of patients with OGIB, definitive treatment with endoscopic interventions, angiographic embolization, or surgical resection continues to remain the mainstay in the initial management of these patients. Supportive management with iron therapy and/or pRBC transfusions is a reasonable option in the subset of patients who have undergone a comprehensive negative diagnostic evaluation; those with recurrent bleeding (without hemodynamic instability) after undergoing endoscopic/radiologic treatment or surgery; and/or those with contraindications for endoscopic/radiologic management or surgery.

Proposed approach to diagnosis and management as follow (Figure 1). A second-look EGD and colonoscopy should be considered in all patients with occult or recurrent overt bleeding due to the high rate of missed lesions. If no bleeding source is identified on conventional endoscopy, small bowel evaluation with CE should be pursued. Therapeutics can then be performed using BAE, as warranted, based upon the type and location of the finding. If the lesion is not ame-
Fig. 1. Proposed approach to diagnosis and management of obscure gastrointestinal bleeding. Dashed arrows indicate less-preferred options. GI, gastrointestinal; EGD, esophagogastroduodenoscopy; CE, capsule endoscopy; CTE, computed tomography enterography; DE, deep enteroscopy; PE, push enteroscopy; SB, small bowel; IOE, intraoperative enteroscopy.7

In patients not amenable to endoscopic treatment, appropriate medical or surgical management should be pursued. In those patients in whom CE is contraindicated due to suspected/known obstruction or stricture, and in patients in whom a tumor is suspected, CT enterography may be the preferred initial test for small bowel evaluation. In the setting of massive bleeding or hemodynamic instability, it would be prudent to proceed with an angiography to localize and treat the bleeding source. Intraoperative enteroscopy should be reserved for patients with severe recurrent bleeding and transfusion dependency and those with a small bowel lesion not accessible with BAE.

Conclusions

OGIB is one of the most challenging problems faced by gastroenterologists due to its evasive nature and relative lack of endoscopic and radiologic tools to facilitate an adequate evaluation of the small bowel. However, the introduction of CE and BAE has served to largely overcome these limitations. With rapidly evolving technology, our ability to diagnose and treat patients with OGIB has improved enormously, resulting in a significant change in the paradigm of the management of OGIB.

References